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Early Identification of Women at Risk of Gestation Diabetes Mellitus

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Editorial

Gestational diabetes mellitus (GDM) is a multifactorial pregnancy complication affecting 1-10% of all pregnancies globally with a rapidly increasing incidence, mainly attributed to advanced maternal age, type 2 diabetes mellitus (T2DM) in pregnant women and the rising prevalence of obesity [1,2]. The disease is defined as any degree of glucose intolerance during gestation and is characterized by insulin resistance as well as decreased insulin secretion caused by reduced pancreatic β- cell function [3].

GDM is associated with short-term adverse maternal and neonatal outcomes, such as the development of preeclampsia, neonatal macrosomia hypoglycemia, jaundice, polycythemia, respiratory distress syndrome, shoulder dystocia, as well as hypocalcemia and preterm birth (Metzger et al., 2008). Women who experience GDM and their offspring are also at increased risk of developing type 2 diabetes, cardiovascular diseases and obesity later in life [4].

Following the recommendations of the World Health Organization and the International Association of Diabetes and Pregnancy Study Groups, diagnosis of GDM is performed with the use of the oral glucose tolerance test (OGTT) in the second trimester of pregnancy, between 24-28 weeks of gestation, allowing limited time for successful intervention. Earlier screening however, ideally in the first trimester of pregnancy when women are enrolled in prenatal care, has the potential to either improve pregnancy outcomes through lifestyle changes and pharmacological interventions or even reduce the frequency of the disease and the severity of the associated maternal and perinatal complications [5,6].

Identification of novel biomarkers for the detection of women destined to develop GDM in early pregnancy, with the potential to either improve the predictive value of current prenatal screening or replace the available methodology is a major goal for researchers in the field of maternal-fetal medicine.

Historically, first trimester prenatal screening for GDM has been performed based on the presence of clinical risk factors, including maternal age, parity, race/ethnicity, body mass index (BMI), family history of diabetes and history of GDM in a previous pregnancy with inadequate specificity and sensitivity. These factors have also been incorporated into multivariate logistic regression models, similar to those used for fetal aneuploidy screening. These methods however, are poor predictors of pregnant women who will develop GDM and are mainly used to identify who should be offered the OGTT to diagnose GDM [7,8].

In order to increase the effectiveness of early prenatal screening for GDM a number of serum biomarkers have been reported that could be used in combination with data from maternal characteristics and medical history. These biomarkers are either markers of placentation [Pregnancy-associated plasma protein A (PAPP-A) and Placental growth factor (PlGF)] or proteins associated with the development of GDM such as glycemic or inflammatory markers and adipocyte derived markers. Even though many of them were thought to be very promising, few have demonstrated potential to be used along with maternal clinical characteristics in order to increase certainty for the detection of GDM during the first trimester of gestation.

The sex hormone-binding globulin (SHBG), a protein closely linked to insulin and insulin resistance has been extensively investigated as a potential biomarker for GDM, since several studies have demonstrated an association between development of GDM and decreased levels of SHBG [9- 11]. Adding SHBG to a prediction model will most likely increase the effectiveness of early GDM prenatal screening but additional validation studies still need to be performed.

Tumor necrosis factor-alpha (TNF-α) is involved in the inflammatory pathway and is another potential marker for insulin resistance during gestation. Studies have shown an increase in TNF-α concentration in maternal serum between 11-13 weeks of pregnancy. However, there has not been an improvement in the prediction of GDM when compared to the assessment of clinical characteristics [12,13]. Increased concentration of C-reactive protein (CRP) in maternal blood during the first trimester of pregnancy has also been associated with the subsequent development of GDM [14]. CRP, however, is closely linked to BMI measurements and therefore it is unlikely that it can provide any additional data beyond the assessment of clinical risk factors for GDM [13].

Adiponectin, a protein originating primarily from maternal adipose tissue has raised significant interest over the years in the research around GDM due to its involvement in metabolism and insulin secretion and sensitivity. In uncomplicated pregnancies, adiponectin levels are known to decrease and are significantly lower in GDM patients [15,16]. In a case controlled study Hedderson et al. reported a 5-fold increase in the risk of development of GDM associated with low levels of adiponectin before pregnancy implying that adiponectin is likely to play a role in the pathogenesis of GDM and could be used for early prediction [17].

In recent years, proteomic technology that allows for the analysis of the global distribution of proteins in pregnancy-related tissues and fluids has provided new opportunities for the identification of novel biomarkers for GDM. In a retrospective case control study, Fruscalzo et al. used proteomics to analyze samples obtained between 12-14 weeks of gestation from 32 pregnant women who subsequently developed GDM along with 64 normoglycemic women as controls [18]. The study revealed reduced transthyretin–retinol-binding

protein–retinol complex (TTR–RBP4–ROH) concentrations in insulin treated GDM cases compared to controls.

Nagalla et al., used the two-dimensional fluorescence difference gel electrophoresis (*2D-DIGE*) and reported elevated glycosylation pattern of fibronectin with Sambucus nigra lectin (SNA) in first trimester maternal serum prior to the onset of hyperglycemia [19]. This finding was further confirmed in a subsequent study by the same group, which evaluated the effectiveness of glycosylated fibronectin levels as a first trimester biomarker for GDM using ELISA [20]. In this study measurement of glycosylated fibronectin levels correctly identified 57 out of 90 pregnant women destined to develop GDM with 63% positive and 95% negative predictive values.

More recently Zhao et al. used the sobaric tags for relative and absolute quantitation (iTRAQ) proteomic technology to analyze samples obtained from 30 women who subsequently developed GDM and an equal number of controls [2]. They identified 33 differentially expressed proteins between the two groups which, based on the gene ontology (GO) analysis, were involved in various signaling processes previously implicated in GDM. The altered expression of four of them namely, apolipoprotein E, coagulation factor IX, fibrinogen alpha chain and insulin-like growth factor-binding protein 5, was further verified by ELISA. The area under the receiver operating characteristic curve (ROC) showed that, combining these four proteins, the sensitivity and specificity for the prediction of GDM were 80% and 95%, respectively suggesting that they may serve as a panel of biomarkers for improving screening performance.

Hence, proteomics studies have clearly demonstrate that biomarkers already exist in maternal circulation at 11-13 weeks of gestation in women who subsequently will develop GDM and have the potential to increase the pool of biomarker candidates. Since currently available candidate proteomic biomarkers have been identified through small in size case control studies, well-designed large scale proteomic studies, following the guidelines of clinical proteomics, are needed to verify these results and possibly discover novel ones for the early detection of women at risk for GDM [21]. These biomarkers may improve early prenatal screening for GDM, further elucidate the mechanisms involved in the pathogenesis of the disease and facilitate the evaluation of early therapeutic interventions for ameliorating short and long term adverse outcomes for the mother and newborn.

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